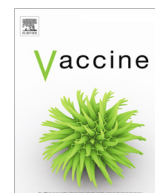




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## Review

# Cost-effectiveness analysis of vaccinations and decision makings on vaccination programmes in Hong Kong: A systematic review



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## ABSTRACT

**Objectives:** To describe and systematically review the modelling and reporting of cost-effectiveness analysis of vaccination in Hong Kong, and to identify areas for quality enhancement in future cost-effectiveness analyses.

**Methods:** We conducted a comprehensive and systematic review of cost-effectiveness studies related to vaccination and government immunisation programmes in Hong Kong published from 1990 to 2015, through database search of Pubmed, Web of Science, Embase, and OVID Medline. Methodological quality of selected studies was assessed using Consolidated Health Economic Evaluation Reporting Standards checklist (CHEERS). Decision making of vaccination was obtained from Scientific Committee on Vaccine Preventable Diseases (SCVPD) and Department of Health in Hong Kong.

**Results:** Nine eligible studies reporting twelve comparative cost-effectiveness comparisons of vaccination programme for influenza ( $n = 2$ ), pneumococcal disease ( $n = 3$ ), influenza plus pneumococcal disease ( $n = 1$ ), chickenpox ( $n = 2$ ), Haemophilus influenzae b ( $n = 1$ ), hepatitis A ( $n = 1$ ), cervical cancer ( $n = 1$ ) and rotavirus ( $n = 1$ ) were identified. Ten comparisons (83.3%) calculated the incremental cost-effectiveness ratio (ICER) of a vaccination strategy versus status quo as outcomes in terms of cost in USD per life-years, cost per quality-adjusted life-years, or cost per disability-adjusted life-years. Among those 10 comparisons in base-case scenario, 4 evaluated interventions were cost-saving relative to status quo while the ICER estimates in 3 of the 6 remaining comparisons were far below commonly accepted threshold and WHO willingness-to-pay threshold, suggestive of very cost-effective. Seven studies were of good quality based on the CHEERS checklist; one was of moderate quality; and one was of excellent quality. The common methodological problems were characterisation of heterogeneity and reporting of study parameters.

**Conclusions:** There was a paucity of cost-effectiveness models evaluating vaccination targeted to the Hong Kong population. All evaluated vaccinations and immunisation interventions in Hong Kong, except for Haemophilus influenzae b, hepatitis A and HPV vaccinations, were considered either cost-saving or very cost-effective when compared to status quo.

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## 1. Introduction

In order to reduce the vaccine-preventable morbidity and mortality, annual costs associated with national routine immunisation programmes in low- and middle-income countries are going to increase from US\$3.5–4.5 billion in 2011 to US\$50–80 billion in 2020 [1]. With scarce resources in public health care system, financial and budgetary impact are the major criteria of decision making processes on which vaccine to introduce and sustain in national immunisation programmes. Theoretically, resources allocated to one emerging vaccine dedicated to one disease population may displace the investment of another health intervention, irrespective of vaccination or not, potentially giving clinical benefits to another disease population.

For equity in access to health services and resources allocation, health economic evaluation including cost-effectiveness analysis and cost-utility analysis is a widely-adopted methodology for assessing the additional value of a new vaccine in current national immunisation programmes. Conclusions from health economic evaluation bring up important information to advisory body for evidence-based recommendation, for example, National Immunisation Technical Advisory Groups (NITAGs) in European countries [2], The Advisory Committee on Immunisation Practices in the US [3], and Australian Technical Advisory Group on Immunisation (ATAGI) [4] in Australia. Apart from health economic evidence, other essential factors such as disease burden, vaccine efficacy and effectiveness, safety, feasibility of programme implementation, ethical and legal considerations also influence the decision making from advisory body and health policy maker [5–8]. In the UK where decision making process is heavily based on absolute incremental cost-effectiveness ratio (ICER) threshold, the value of vaccine for the gain in health of their populations is evaluated by Joint Committee on Vaccination and Immunisation (JCVI) and compared against country-specific threshold value to inform decision making. Efficacious and effective vaccinations are more likely to be incorporated into national immunisation programme in condition when health service is willing to pay for vaccine adoption to routine practice.

In Hong Kong context, the Scientific Committee on Vaccine Preventable diseases, under the Centre for Health Protection [9], has the responsibility of reviewing the up-to-date evidence from both local data and overseas practice, and providing scientific advice and recommendations on strategies for government immunisation programmes in local population [9]. Three universal vaccination programmes (Childhood Immunisation Programme, Government Vaccination Programme, and Residential Care Home Vaccination Programme) have been officially implemented by Department of Health. Under Childhood Immunisation Programme, children have been required to receive at least 12 injections before Primary Six since February 2007 to prevent nine infectious diseases including tuberculosis, poliomyelitis, hepatitis B, diphtheria, pertussis, tetanus, measles, mumps and rubella [10]. Since September 2009, four doses of pneumococcal vaccine have been added to the vaccination schedule for children aged two months, four months, six months and 12 months, respectively. Varicella-containing vaccine for prevention of chickenpox infection was recommended to be

scheduled in Childhood Immunisation Programme since 2012, and added to Childhood Immunisation Programme for infant since June 2014 [11]. Completing the routine childhood immunisation programme is a requirement for school entry in Hong Kong whilst the coverage rates of these compulsory vaccines were over 99% among Hong Kong-born children [11]. The decision making of Childhood Immunisation Programme seems to follow the World Health Organization's recommendations [12] but excludes influenza, rotavirus and *Haemophilus influenzae* b (Hib) vaccines which are available on the private market because of a hybrid public-private healthcare system in Hong Kong [13]. The infant and elderly were recommended to undertake 23-valent pneumococcal polysaccharide vaccine since 2007. The 7-valent pneumococcal conjugate vaccination (PCV-7) was incorporated in Childhood Immunisation Programme for infant since 2007, and subsequently replaced by pneumococcal polysaccharide vaccine with serotype coverage, 10-valent (PCV-10) in 2010 and 13-valent (PCV-13) in 2011. Such changes in decision-making seem to be associated with increasing availability of local epidemiological data, continuously reviewing of vaccine safety and efficacy, and overseas experience [9]. Both the trivalent and quadrivalent influenza vaccines for prevention of seasonal flu were provided by public clinics and hospitals under the Government Vaccination Programme and Residential Care Home Vaccination Programme, and private doctors under Vaccination Subsidy Scheme. However, the public health objectives for the inclusion or exclusion of certain groups for influenza vaccination prioritization are not clearly stated. Overall, group prioritization for influenza vaccination may be based on risk of infection (e.g., young children and poultry workers), risk of severe disease if infected (e.g., pregnant women) and risk of transmission to other vulnerable people (e.g., healthcare workers, young children, and elderly living in residential care homes) [14] with data from surveys of public demands among the potential target groups and may also take into account aspects of cost-benefit and cost-effectiveness.

Although Hong Kong is considered as a region in high-income counties, decision making process was calling for transparency to the general public and health professional for critical appraisal [15]. Recent systematic review [16] linking ICER values of evaluated interventions to government's decisions suggested that the ICER values may be associated with advisory body's decision to inform recommendation. Nevertheless, the impact of cost-effectiveness analysis of vaccination on decision making was uncertain. A single ICER threshold value for decision making on which vaccination to recommend and accept in public health care system is not officially available in Hong Kong, besides the gross domestic product per capita threshold recommended by World Health Organisation [17].

Reporting standard, characteristics and assumption of cost-effectiveness models evaluating vaccination influence the base-case results, contributing to decision making on funding for national immunisation programme. Following the World Health Organisation guideline and consensus [18,19], critically appraisal on whether methodology is properly analysed and adequately presented is a vital step before considering results and consequent recommendations. Heterogeneity in modelling approaches and

assumptions across studies [20,21] was identified, even for models evaluating the same vaccination. Recent systematic reviews explicitly focused on the modelling aspects and results of cost-effectiveness evaluation of vaccination in low- and middle-income countries [22,23]. Results in a majority of studies considered the vaccination to be either cost-saving or very cost-effective.

The aims of this systematic review were (1) to review published cost-effectiveness studies of vaccination in Hong Kong, and the reporting quality of those studies, (2) identify areas for quality enhancement of future cost-effectiveness studies, and (3) explore whether cost-effective evidence of vaccination was associated with decisions making about the recommendation and acceptance of a particular vaccination into government immunisation programmes in Hong Kong.

## 2. Method

### 2.1. Systematic literature search on cost-effectiveness models in Hong Kong

#### 2.1.1. Selection criteria

The eligibility criterion of studies was to evaluate the cost-effectiveness of vaccination and immunisation interventions against the status quo (i.e. existing vaccination policy and clinical practice) as the comparator. Articles without available full text or full report were excluded. If there were duplicated articles or reports, the most complete work done by authors was selected. After the initial check for duplicated articles, the abstracts of remaining articles were screened by authors (CW and VG) to exclude editorials, letters, commentaries, study protocols, case reports, pure literature reviews and meta-analyses, conference proceedings, past and current clinical guidelines, and recommendations.

#### 2.1.2. Search engines and strategies

A systematic and comprehensive literature search was conducted in databases of PubMed, Web of Science using the Web of Knowledge platform, Embase, and MEDLINE using the Ovid searching platform to identify studies that investigated the economic evaluation of health interventions to be considered in public clinical setting in Hong Kong. The Medical Subject Heading “Hong Kong”, “China”, and “Chinese” were combined with “cost-effectiveness”, “cost-effective”, “cost-benefit”, “cost-utility”, “cost-minimization”, “cost-minimisation”, “cost-saving”, “willingness-to-pay” and “economic evaluation”. Studies were limited to English language and the publication years between 1990 and 2015. The earliest year was chosen as 1990 because the concept of value for money in health emerged around early-1990s [24]. Such searching strategies were adopted from a previous literature review [16] on the health technology assessment of cancer screening strategies in Hong Kong. All searches were performed within the University of Hong Kong during March 2015.

#### 2.1.3. Quality assessment

Methodological quality of the included studies was assessed according to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist [25], which was adopted as the evaluation of reporting standard of health economics analysis. The CHEERS checklist contains 24 criteria assessing different aspects of quality and reporting standard of economic evaluations: background and objectives, target population and subgroups, setting and location, study perspective, comparators, time horizon, discount rate, choice of health outcomes, measurement of effectiveness, measurement and valuation of preference based outcomes, estimating resources and costs, choice of model,

assumptions, analytical methods, study parameters, incremental costs and outcomes, characterising uncertainty, characterising heterogeneity, study findings, limitations, generalisability, source of funding, and conflicts of interest. For each included study, each reporting quality criterion was rated as “yes” with a score of 1 or “no” with a score of 0 to indicate if the quality criterion was met or not for each criterion, respectively. Furthermore, overall quality rating of included studies was scored on a four-point Likert scale in a descending order of “excellent”, “good”, “moderate” or “low” quality when study fulfilled 100%, >75–<100%, >50–≤75%, or ≤50% of the criteria, respectively. Articles with “low” reporting standard that lack transparency and clarity were further excluded from subsequent analyses. This classification has been used in previous systematic reviews of health economic evaluations [26,27].

#### 2.1.4. Data extraction

A standardized form was used when extracting the data reported in included studies. The primary data extracted from each article involved: first authorship, year of publication, design or type of economic evaluation, targeted disease (influenza, pneumococcal disease, chickenpox, Hib, hepatitis A, cervical cancer and rotavirus), targeted population (infant aged < 1, children aged 1–17, elderly aged 65 or above, girls aged 10–17, and general population), comparator, study perspective, year cost, price of vaccine, clinical data source, modelling approaches, sensitivity analysis performed, and cost-effectiveness outcomes. Modelling characteristics included type of models (Markov model, decision tree, discrete-event simulation, dynamic model or no models), time horizons, discount rate, preference valuation, and sensitivity analysis. Each health economic assessment of vaccination strategy versus the comparator was defined as one comparative cost-effectiveness analysis. For each pairwise cost-effectiveness comparison, we obtained the ICER value at base-case scenario, as expressed in cost per event cases prevented, cost (USD) per life years gained, cost per QALYs gained, or cost per disability-adjusted life years (DALYs) averted of one vaccination strategy relative to the comparator. Conclusion of included studies was grounded on the ICER value at base-case scenario. Costs in each strategy and ICER value for each pairwise cost-effectiveness comparison were not adjusted for year of valuation.

## 3. Results

Fig. 1 lists the process of literature identification, abstract screening for eligibility, and selection of original studies during the literature and hand search presented in a Preferred Reporting Items for Systematic Reviews and meta-Analyses flow diagram [28]. Systematic database search identified 1335 potentially relevant studies (PubMed: 446; Web of Science: 232; MEDLINE: 300; and Embase: 357) that met the searching criteria in four research databases. After the removal of duplicated ( $n = 544$ ) and non-original articles ( $n = 237$ ) by abstract screening, the full-text of 70 studies were assessed for eligibility. Among them, 62 were not related to vaccination and one did not focus on cost-effectiveness analysis of vaccination [29]. Based on bibliographic database search, seven cost-effectiveness analyses related to vaccination in Hong Kong were included. A total of nine studies, seven from bibliographic databases and two from hand searches, was finally included in this systematic review. The earliest study was published in year 2001.

Table 1 summarizes description and modelling characteristics of included studies. Nine eligible studies reporting twelve comparative cost-effectiveness comparisons of vaccination and immunisation programme for influenza ( $n = 2$ ), pneumococcal disease ( $n = 3$ ), influenza plus pneumococcal disease ( $n = 1$ ), chickenpox

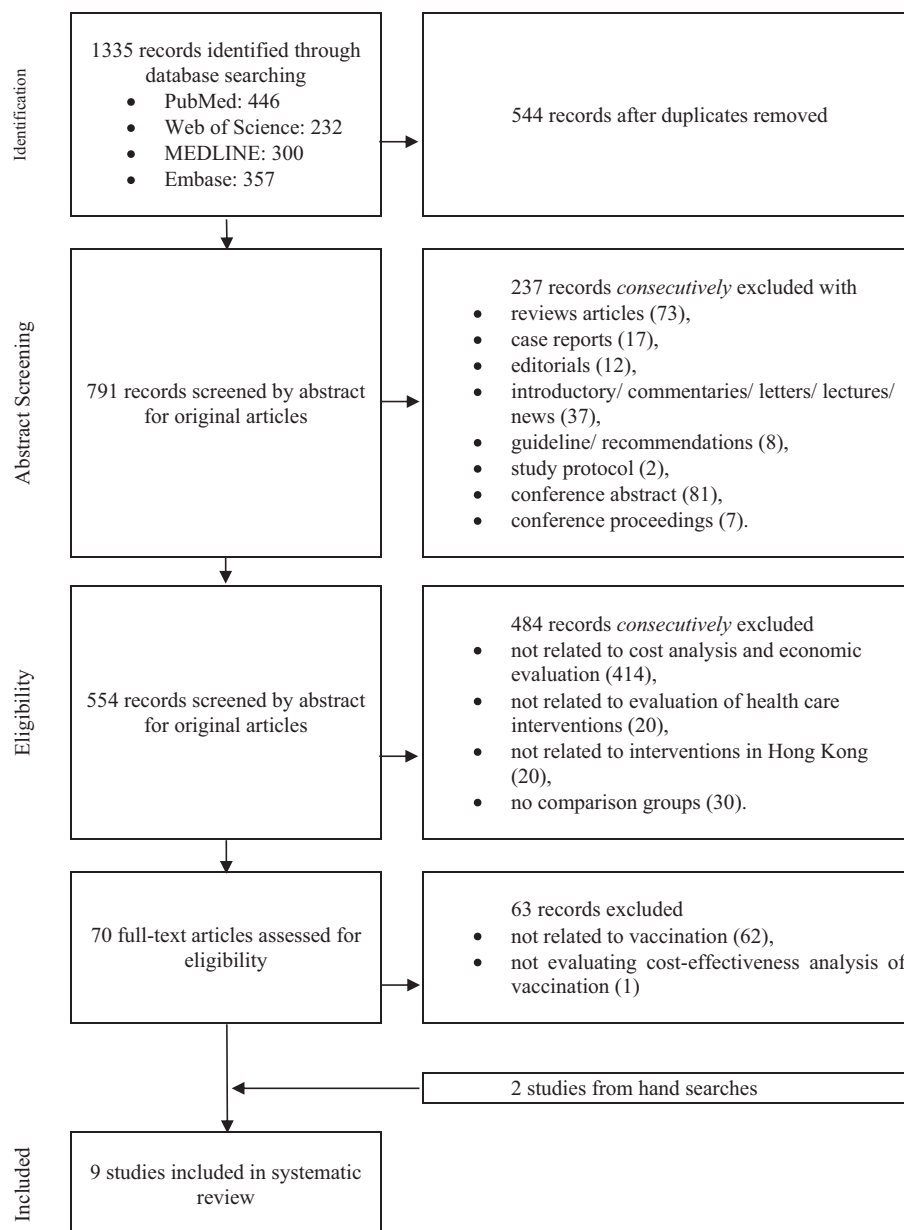


Fig. 1. PRISMA Flow Diagram of the literature search and selection process.

( $n = 2$ ), Hib ( $n = 1$ ), hepatitis A ( $n = 1$ ), cervical cancer ( $n = 1$ ) and rotavirus ( $n = 1$ ) were identified. No vaccinations except for chickenpox, influenza, and pneumococcal disease, were implemented in government immunisation programme. Two-third ( $n = 6$ ) of studies disclosed no funding or non-industry funding. Most studies established a Markov model (33.3%), evaluated from the perspective of health care provider (33.3%) or societal (33.3%), reported an ICER of vaccination strategy versus the comparator in effectiveness unit of QALY only (55.6%), applied an annual discount rate of 3.0% (55.6%), performed probabilistic sensitivity analysis (55.6%), and adopted list price or acquisition price of vaccine (55.6%). Time horizon applied in modelling varied between studies.

Evaluated vaccination, comparators, target disease population and main results of studies are found in Table 2. Evaluated vaccinations included varicella vaccine, influenza programme particularly for quadrivalent influenza and trivalent influenza, pneumococcal vaccine for 7-valent, 10-valent and 13-valent conjugates, rotavirus,

human papillomavirus vaccination (HPV) and combined vaccines for the Hib, chickenpox, pneumococcal, and hepatitis A. Pneumococcal vaccinations were evaluated in infant and elderly. Two cost-effectiveness comparisons reported the 'influenza-like illness case prevented' [30] or 'Benefit-to-cost ratio' [31] as the only effectiveness unit, in which health economic outcome was not expressed as ICER value to compare against ICER threshold for recommendation. Out of the remaining ten comparisons, four comparisons demonstrated a negative ICER value as a result of cost-saving [32–35] and six comparisons reported ICER values from USD500 to USD3,525,635 where available [36,37]. Particularly for those studies reporting positive ICER values, the universal PCV-7 vaccination targeting to infant pneumococcal disease was regarded as cost-effective with an ICER value of USD6460 per life year gained while the influenza and pneumococcal vaccination targeting to elderly subjects was also considered as cost-effective with an ICER value of USD500 per QALY gained. The ICER values of



**Table 1**

Description and modelling characteristics of nine included studies.

	n	(%)		n	(%)
Year of publication			Reporting of ICER		
2000–2005	1	(11.1)	LY only	1	(11.1)
2006–2010	4	(44.4)	QALY only	5	(55.6)
2011–2015	4	(44.4)	LY & QALY	1	(11.1)
Funding source			Others or not reported	2	(22.2)
Industry	1	(11.1)	Model type		
Non-industry	3	(33.3)	Decision Tree	2	(22.2)
No funding	3	(33.3)	Decision-analytic model	1	(11.1)
Non-disclosed	2	(22.2)	Markov model	3	(33.3)
Types of economic evaluation			Epidemiology model	1	(11.1)
Cost-utility	6	(66.7)	Markov & dynamic model	2	(22.2)
Cost-effectiveness	3	(33.3)	Time horizon		
Disease population			80-year	1	(11.1)
Chickenpox	1	(11.1)	50-year	1	(11.1)
Influenza	2	(22.2)	10-year	2	(22.2)
Pneumococcal disease	2	(22.2)	9-year	1	(11.1)
Influenza & pneumococcal disease	1	(11.1)	5-year	2	(22.2)
Rotavirus	1	(11.1)	Not reported	2	(22.2)
Hib, chickenpox, pneumococcal & hepatitis A	1	(11.1)	Year cost		
Cervical cancer	1	(11.1)	2001–2005	1	(11.1)
Target population			2006–2010	3	(33.3)
Infant	4	(44.4)	2011–2015	2	(22.2)
Elderly ( $\geq 65$ years)	2	(22.2)	Not reported	3	(33.3)
Pediatric	1	(11.1)	Annual discount rate		
Girls (10–17y)	1	(11.1)	0.0%	1	(11.1)
Elderly (65–80 yr), Children (1–15 yr) & Working age	1	(11.1)	3.0%	5	(55.6)
Study Perspective			5.0%	2	(22.2)
Healthcare provider	3	(33.3)	Not reported	1	(11.1)
Societal	3	(33.3)	Preference or utility valuation		
Payer	1	(11.1)	By assumption	6	(66.7)
Payer & societal	1	(11.1)	No calculation of QALY	3	(33.3)
Healthcare provider & societal	1	(11.1)	Sensitivity analysis		
Price of Vaccine			Deterministic	3	(33.3)
List or acquisition price	5	(55.6)	Probabilistic	5	(55.6)
Not reported	4	(44.4)	No	1	(11.1)

Note: Hib = Haemophilus influenzae b; ICER = Incremental cost-effectiveness ratios; LY = life-year; QALY = quality-adjusted life-year.

universal PCV-7, Hib, and hepatitis A vaccination targeting to infant were USD7564, USD20,725, and USD3,525,635 per life year gained, respectively [31]. Adding HPV vaccination for 12-year old girls had an ICER value of USD11,732–USD14,202 per QALY gained [38]. All evaluated vaccinations, except for HPV, Hib and hepatitis A [31] vaccinations, were considered either cost-saving or very cost-effective based on conclusions of included studies in Hong Kong. Those cost-effective or recommended vaccinations, except for one evaluating the universal rotavirus vaccination for infant [33], was included in government immunisation programme. Therefore, cost-effective evidence from published studies and reports appeared to be associated with decision-making from government.

Table 3 shows the reporting quality of each study represented by the scoring of the CHEERS checklist. Seven studies were of good quality based on the CHEERS checklist [31–37], one was of moderate quality [30], one was of excellent [38], and none was of low. In summary, 19 out of the 24 items were fulfilled by >80% of the studies except in the items of time horizon (item 8), study parameters (item 18), characterising heterogeneity (item 21), source of funding (item 23) and conflicts of interest (item 24). In particular, two studies met the quality criteria of characterising heterogeneity, and explained variations in cost, outcomes or cost-effectiveness between subgroups. Two [30,32] of the nine studies did not mention the time horizon over which costs and consequences were being evaluated. Two studies [30,33] did not describe any potential for conflicts of interest of study contributors. Two studies [35,36] did not clearly state the funding sources, denoted as ‘non-disclosure’, while one study [34] out of seven remaining studies declared the support from industry-

sponsorship. Three studies [30,34,37] did not state the study parameters like values, ranges, references and probability distributions for all parameters.

#### 4. Discussions

This systematic review synthesized the cost-effective evidence and appraised the reporting quality of published cost-effectiveness analysis of vaccination in Hong Kong. The principal findings based on published evidence was that all evaluated vaccination and immunisation interventions, except for Hib, hepatitis A and HPV vaccinations, were considered either cost-saving or very cost-effective when compared to status quo, in line with health economic evidence reported in previous systematic reviews [21,23]. Evidence from this review did not draw conclusion on whether the ICER values were associated with decision-making of government to recommend and implement the vaccination and immunisation programme in Hong Kong. Interestingly, all cost-effective or recommended vaccinations except for universal rotavirus vaccination were included in government immunisation programme. Despite that universal rotavirus vaccination was considered as cost-saving strategy in the literature, rotavirus vaccine is neither been recommended by SCVPD [9] nor included in Hong Kong Childhood immunisation programme for implementation [11]. To an extent, the ICER values of four cost-effectiveness comparisons were not available [32–35], due to dominance or cost-saving. Merely one out of four dominated vaccinations was neither recommended nor implemented; leading to the notion that cost-effective evidence may be associated with the recommendation

**Table 2**

Evaluated vaccinations, comparators, target disease and population, and main results of nine studies.

First author	Year	Funding source	Design / type of econ-evaluation	Target disease	Intervention	Comparators of intervention	Target population	Study Perspective	Source of clinical data			
Chui	2014	No funding	Cost-utility	Chickenpox	Varicella vaccine as post-exposure prophylaxis	No vaccination	Pediatric (1-18y)	Healthcare provider	Local cohort data and overseas literature			
Fitzner	2001	No funding	Cost-effectiveness	Influenza	Influenza prevention programme	No vaccination	Elderly (65-80y) Children (1-15y) Working-age Infant	Societal	Local surveillance and cohort data			
Ho	2008	Non-industry	Cost-effectiveness	Rotavirus	Universal rotavirus vaccination	No vaccination	Infant	Healthcare provider	Local cohort data and overseas literature			
Lee	2009	Non-disclosed	Cost-effectiveness	Pneumococcal disease	Universal PCV-7 vaccination	No vaccination	Infant	Payer & societal	Local cohort data and overseas literature			
Lee	2013	Industry	Cost-utility	Pneumococcal disease	Universal PCV-10 vaccination versus universal PCV-13 vaccination	Universal PCV-13 vaccination	Infant	Payer	Local literature only			
You	2009	Non-disclosed	Cost-utility	Influenza and pneumococcal disease	Influenza and pneumococcal vaccination	No vaccination	Elderly (≥65 y)	Healthcare provider	Local cohort data and overseas literature			
You	2014	No funding	Cost-utility	Influenza	Quadrivalent influenza vaccine versus trivalent influenza vaccine	Trivalent influenza vaccine	Elderly (≥65 y)	Societal	Local cohort data and overseas literature			
McGhee	2008	Non-industry (commissioned by government)	Cost-utility	Hib, chickenpox, pneumococcal, hepatitis a	Combined vaccines for the Hib, chickenpox, pneumococcal, and hepatitis A	No vaccination	Infant	Healthcare provider & societal	Local cohort data and overseas literature			
Wu	2012	Non-industry (commissioned by government)	Cost-utility	Cervical cancer	Human papillomavirus vaccination	No vaccination	Girls (10–17 y)	Societal	Local surveillance and cohort data			
First author	Year	Reporting of cost-effectiveness outcomes				Conclusions	Type of Model	Time horizon	Year cost	Price of vaccine	Discount rate	Sensitivity analysis
		ICER	LY	QALY	Others							
Chui	2014	Yes	No	Yes	No	Varicella vaccine as post-exposure prophylaxis was cost-saving	Decision tree	NR	NR	List price	0%	Probabilistic
Fitzner	2001	No	No	No	Influenza-like illness case prevented	Influenza vaccine was cost-effective from the perspective of a susceptible Individual but not from societal perspective	Decision tree	NR	NR	List price	NR	Deterministic
Ho	2008	Yes	No	No	DALY averted	A universal rotavirus vaccination was cost-saving	Markov model	5-year	2002	NR	3%	Probabilistic
Lee	2009	Yes	Yes	No	IPD prevented	Routine infant vaccination with PCV-7 was cost-effective	Decision-analytic model	10-year	2006	NR	5%	Deterministic
Lee	2013	Yes	No	Yes	IPD prevented	PCV-10 vaccination was a cost-saving strategy compared with PCV-13 vaccination	Markov model	10-year	2011	NR	5%	Probabilistic
You	2009	Yes	No	Yes	No	Influenza vaccination with or without pneumococcal vaccination was cost-saving	Markov model	5-year	2006	List price	3%	Probabilistic
You	2014	Yes	No	Yes	No	Quadrivalent influenza vaccine was cost-effective	Epidemiology model	9-year	2014	NR	3%	No
McGhee	2008	Yes	Yes	Yes	Benefit-to-cost ratio	Pneumococcal vaccine showed more benefit than costs. Hib vaccine was cost-effective given using a very conservative model. Varicella and hepatitis A vaccines had uncertainties on cost-effectiveness	Markov model and dynamic model (for Varicella)	80-year	NR	List price	3%	Deterministic
Wu	2012	Yes	No	Yes	No	HPV vaccination of 12-year-old girls was a cost-effective addition to current cervical cancer prevention guidelines	Markov model and dynamic model	50-year	2010	List price	3%	Probabilistic

Note: ICER = incremental cost-effectiveness ratio; LY = life-years; QALY = quality-adjusted life-years; DALY = disability-adjusted life-years; IPD = invasive pneumococcal disease; Hib = Haemophilus influenzae b; HPV = human papillomavirus; NR = not reported.

**Table 3**

Reporting standards of nine included health economic evaluation studies.

First author Publication year	Chui 2014	Fitzner 2001	Ho 2008	Lee 2009	Lee 2013	You 2009	You 2014	McGhee 2008	Wu 2012	Total % of Yes
<i>CHEERS statement item number</i>										
1 Title	1	1	1	1	1	1	1	1	1	100%
2 Abstract	1	1	1	1	1	1	1	1	1	100%
3 Background and objectives	1	1	1	1	1	1	1	1	1	100%
4 Target population and subgroups	1	1	1	1	1	1	1	1	1	100%
5 Setting and location	1	1	1	1	1	1	1	1	1	100%
6 Study perspective	1	1	1	1	1	1	1	1	1	100%
7 Comparators	1	1	1	1	1	1	1	1	1	100%
8 Time horizon	0	0	1	1	1	1	1	1	1	78%
9 Discount rate	1	0	1	1	1	1	1	1	1	89%
10 Choice of health outcomes	1	1	1	1	1	1	1	1	1	100%
11 Measurement of effectiveness	1	1	1	1	1	1	1	1	1	100%
12 Measurement and valuation of preference based outcomes	1	0	1	1	1	1	1	1	1	89%
13 Estimating resources and costs	1	1	1	1	1	1	1	1	1	100%
14 Currency, price date, and conversion	1	0	1	1	1	1	1	1	1	89%
15 Choice of model	1	1	1	1	1	0	1	1	1	89%
16 Assumptions	1	1	1	1	1	1	1	1	1	100%
17 Analytical methods	1	1	1	1	1	0	1	1	1	89%
18 Study parameters	1	0	1	1	0	1	0	1	1	67%
19 Incremental costs and outcomes	1	1	1	1	1	1	1	1	1	100%
20 Characterising uncertainty	1	1	1	1	1	0	1	1	1	89%
21 Characterising heterogeneity	0	1	0	0	0	0	0	0	1	22%
22 Study findings, limitations, generalizability, and current knowledge	1	1	1	1	1	1	1	1	1	100%
23 Source of funding	1	1	1	0	1	0	1	1	1	78%
24 Conflicts of interest	1	0	0	1	1	1	1	1	1	78%
% of Yes	92%	75%	92%	92%	92%	92%	79%	96%	100%	
Overall quality	Good	Moderate	Good	Good	Good	Good	Good	Good	Excellent	90%

Note: "1" Meets the quality assessment criteria, "0" does not fully conform to the quality assessment criteria.

CHEERS - Consolidated Health Economic Evaluation Reporting Standards.

and implementation of vaccination in Hong Kong. Therefore, in addition to cost-effective evidence, other practical considerations such as disease prevalence, vaccine efficacy, budgetary constraints and public acceptance were also taken into account when making recommendation and funding decision by government.

The use of CHEERS checklist allows consistent and fair comparisons of quality reporting across studies. Overall reporting quality was good when appraising the quality assessment criteria outlined in CHEERS checklist and one of the studies was rated as excellent in overall quality. Reporting quality of studies was gradually improved from 'moderate' to 'good' or 'excellent' quality standard over the years. In order to achieve the 'excellent' quality standard, subgroup analysis which reports variability across subgroups should be conducted in future health economic evaluations.

Most studies utilized the local real-world cohort data and overseas literature as source of clinical data but the clinical data source of remaining three studies [30,34,38] was primarily based on assumption and local data only. This was in part due to the lack of epidemiological cohort data to estimate the natural history of disease progression and burden, and randomized controlled trial data to estimate the adverse effects and efficiency of vaccine in Hong Kong. Moreover, most studies adopted the acquisition costs or market prices as the price of vaccine but the type of vaccine price was unstated for the remaining studies. Varying the amount of vaccine price had impact on results of cost-effectiveness analysis. With the demand for the transparency of vaccine price, WHO has set out a comprehensive web platform [39] which provides information on average vaccine price for countries of all income groupings.

With respect to methodological and modelling aspects, health economic outcomes were mostly modelled by static modelling like Markov models and decision trees. By principle, model type has to be adequately chosen depending upon targeted disease population [40]. Future models simulating health economic impact of vaccinations for infectious diseases, e.g. seasonal influenza, human papillomavirus and chickenpox, should be established using

transmission dynamic modelling approach accounting for direct benefit of prevention of disease transmission between individuals within the community due to vaccination, indirect benefit of herd immunity effects, and the change in parameter values over time [20]. This review identified two studies [31,32] applying different modelling approaches to evaluate the cost-effectiveness of varicella vaccine. Chui et al. [32] applying the static modelling approach expressed the health benefits in QALY whilst the earlier report [31] establishing dynamic modelling demonstrated benefit-to-cost ratio for such cost-effectiveness comparison. Hence, comparisons in results between static and dynamic models are warranted.

Role of industry-sponsorship may lead to a publication bias which was in favour of vaccine products developed by sponsors, as recognized in systematic review of economic evaluations on pneumococcal vaccines conducted in European countries [41]. Conclusion of one industry-sponsored study [34] reported that the universal PCV-10 vaccination targeting to infant pneumococcal disease was dominant strategy relative to universal PCV-13 vaccination. Nevertheless, one recent industry-sponsored study [42], out of the scope of searching period, found universal PCV-13 vaccination was a better option than PCV-10 vaccination and no vaccination, contradictory to previous modelling study with PCV-10 in comparison to PCV-13 vaccination [34]. Researchers are urged interpreting findings of industry-sponsored studies with caution. Among two studies which were not disclosed with any funding [35,36], conclusions were considered evaluated vaccination as cost-effective. For those indicating either no funding or non-industry funding, evaluated vaccination was dominant strategy. Collectively, influence of industry-sponsorship on conclusion was not evident in this review, calling for more cost-effectiveness analyses to ascertain whether the sponsorship effect did exist or not. On one hand, recommendations from studies [31,38] commissioned by government heavily influenced the decision making of whether the vaccine is included in government immunisation programme. In the commissioned study published in 2008 [31], pneumococcal vaccine was recommended to be included in



Childhood Immunisation Programme which subsequently incorporated PCV-7 vaccination in 2009 [11]. Besides the funding source, there was a paucity of published cost-effectiveness models evaluating meningococcal, Japanese encephalitis and herpes zoster vaccinations targeted to Hong Kong population. As such, we urged further research in health economic evaluations of emerging vaccinations, if applicable to Hong Kong setting.

Systematic reviews of vaccinations in a low- and middle-income countries context highlighted the variability of the ICER threshold used for different studies in the same country [22], and hence emphasized the need for ICER threshold value for decision making [43]. However, estimation of willing to pay for vaccination and an ICER threshold value of vaccination adoption decision making in Hong Kong as high-income country was not possible, in contrast to previous pooled analyses revealing that the increase in ICER value was associated with a lower likelihood of positive past decision [44,45].

## 5. Conclusions

There was a paucity of cost-effectiveness models evaluating vaccination targeted to Hong Kong population. All evaluated vaccinations and immunisation interventions in Hong Kong, except for Hib, hepatitis A and HPV vaccinations, were considered either cost-saving or very cost-effective when compared to status quo, based on findings reported from included studies. Cost-effective evidence may be associated with the recommendation and implementation of vaccination in Hong Kong. Future studies evaluating the cost-effectiveness of vaccination in Hong Kong should improve the reporting quality, especially list of study parameters, and conduct subgroup analysis and dynamic modelling for simulation.

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## Conflict of interest

None declared.

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